REMARKS

The Office Action has rejected Claim 72 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. It has also rejected Claims 38, 43, 44, 46, 47, 54-56, 59, 60, 63-66 and 71-73 under 35 U.S.C. § 102(b) as defining subject matter which is allegedly anticipated by the teachings of U.S. Patent No. 6,126,969 to Shah et al. Claims 38, 43, 54-56, 59, 60 and 71-73 are rejected under 35 U.S.C. § 102(b) as defining subject matter which is allegedly anticipated by the teachings in U.S. Patent No. 6,387,403 to Seroft et al. (Seroft et al.). Further, the Office Action has rejected Claims 38, 43, 44, 46, 47, 54-56, 59, 60, 63-66 and 71-73 under 35 U.S.C. § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,416,786 to Mulye et al. ("Mulye et al."). Moreover, Claims 38, 43, 44, 46-48, 54-56, 59, 60 and 63-73 are rejected under 35 U.S.C. § 103(a) as defining subject matter which is allegedly rendered obvious by the teachings of Shah et al. and further in view of the teachings in an article by Tobyn et al. in Inr. J. Pharm. 1998 169, 183-194 ("Tobyn et al."). In addition, Claims 38, 43-47,54-56, 59, 60, 63-66 and 71-73 are rejected under 35 U.S.C. § 103 (a) as defining subject matter which is allegedly unpatentable over the teachings in Seroff et al. in view of the teaching in U.S. Patent No. 6,340,475 to Shell et al. ("Shell et al."). In addition, Claims 38, 40-48, 54-56, 59, 60 and 63-73 are rejected under 35 U.S.C. § 103 as defining subject matter which is rendered obvious by the teachings of Seroff et al. and Shell et al. and further in view of the teachings by Tobyn et al.

Applicants have amended the application and specification. In particular, applicants have amended the specification in Paragraph 40 to correct an obvious typographical error. Further applicant has amended Claim 38 by inserting an "about" before 1:50. Support is found in Paragraph 48. In addition, applicant has cancelled the non-elected claims without

prejudice. Applicant has not abandoned the subject matter in the non-elected claims and reserves the right to file a divisional application directed thereto.

No new matter has been added to the application.

Pursuant to the rejection of Claim 72, the Office Action alleges that placing a comma between the terms "soluble alginate" and "methyl cellulose" is new matter. Applicant disagrees. The placement of a comma between soluble alginate and methyl cellulose is to correct an obvious typographical error. This error was corrected in the specification in Paragraph 40 thereof. In view of the correction in the specification, there is antecedent basis for the previous amendment to Claim 72.

Pursuant to the rejection of Claims 38, 43, 44, 46, 47, 54, 56, 59, 60, 63-66 and 71-73 the Office Action cites Shah et al.

The present invention is directed to, inter alia, a sustained release pharmaceutical composition in oral dosage form comprising in the core thereof a mixture comprising a pharmaceutically effective amount of a drug, a sustained release carrier in an effective amount to retard the release of the drug from said composition when placed in an aqueous system, a water insoluble or partially water insoluble cellulose, maltodextrin and optionally a lubricating effective amount of a lubricant, wherein the weight ratio of cellulose to maltodextrin ranges from about 50:1 to about 1:50. As described in the specification, the sustained release polymer influences the release of the drug from the formulation. However, this release can be fine tuned by the additional combination of maltodextrin and the water insoluble or partially water soluble cellulose, such as microcrystalline cellulose, silicified microcrystalline cellulose, and the like. As noted by Applicant in Paragraph 46 of the instant application, the presence of the excipient, the water insoluble or partially water soluble cellulose had made it difficult to formulate

controlled release tablets because they cause the disintegration of the tablet when in contact with an aqueous solution, causing the release of the medicament to be more rapid than desired. However, the inventor has found that this effect can be counteracted by the addition of maltodextrin. Thus, the present invention requires the interaction of maltodextrin with the water insoluble or partially water soluble cellulose and the interaction of both with the sustained release polymer and the drug. Thus, all four of these components need to be in the core so that they can interact directly.

If the maltodextrin were not present in the core, e.g., it could not interact with the water insoluble cellulose or partially water insoluble cellulose and counteract its effect in accelerating the release of the drug in the formulation. The cited prior art, in combination do not teach, disclose or suggest the presence of all four components in the core.

Shah et al. disclose an orally administrable combination immediate release/sustained release tablet comprising a compressed homogenous mixture of uncoated particles of an active pharmaceutical ingredient and particles of that same ingredient which are coated with a polymer material which is pH independent, water insoluble and water permeable, the coated particles being present in an amount which is effective to provide a sustained therapeutic effect and the uncoated particles being present in an amount which is effective to provide an immediate therapeutic effect.

The Office Action refers to the formulations in Table 1 and Table 2 of Shah, alleging that Shah et al. disclose the present composition. However, Tables 1 and 2 refer to the composition described in Examples 1 and 2, respectively in Shah et al. Example 1 discloses that microcrystalline cellulose is mixed with a sustained release coated acetaminophen containing acetaminophen, isononyl phenyl polyoxyethylene glycol ethers, methacrylate ethers and talc, and

then mixing acetaminophen and microcrystalline cellulose with crosslinked PVP and uncoated acetaminophen. It further teaches that the uncoated acetaminophen is comprised primarily of acetminophen and contains minor amounts of maltodextrn and PVP. Thus, in Example 1 the microcrystalline cellulose is present with sustained release coated acetaminophen, while the maltodextrn is present in a different layer, with the immediate release acetaminophen. Thus, the maltodextrn in Example 1 cannot interact with the microcrystalline cellulose, which is unlike the present invention.

Example 2 indicates that the tablet is prepared in accordance with the procedure in Example 1. Thus, in Example 2, the microcrystalline cellulose cannot interact with the maltodextrin.

Case law has held that anticipation requires a single source to contain all of the elements in the claim. Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F2d 1367, 1379, 231 USPQ 81, 90 (Fed Cir 1986). Further, the single source must disclose all of the claimed elements arranged as in the claims. Richardson v. Suzuki Motor Co., 868 F2d 1226, 1238, 9 USPQ 2d 1913, 1920 (Fed Cir 1989).

Here, Shah et al. do not arrange the elements as in the claim. The claim requires that the drug, the water insoluble cellulose or partially water insoluble cellulose, sustained release polymer and maltodextrin to be present and mixed together in the core of the tablet. However, in Shah, the cellulose ether and the maltodextrin are contained in different layers. The maltodextrin is not part of a sustained release formulation. The drug, the cellulose, maltodextrin and sustained release polymer are not present in the core, as claimed. Since all of the elements in Shah et al. are not arranged as in the claim, Shah et al. do not anticipate the present invention. Therefore, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 45, 54-56, 59, 60 and 71-73 under 35 U.S.C. § 102(b), the Office Action cites Seroff et al.

Seroff et al. disclose an osmotic dosage form adapted to release reboxetine at a uniform rate comprising

(a) a semipermeable membrane defining an internal compartment;

(b) an osmotic composition component comprising reboxetine and a carbohydrate within the internal compartment and

(c) a delivery orifice formed or formable in the semipermeable membrane through which the roboxetine is delivered.

The Office Action refers to Figure 2 and Example 4B. Figure 2 represent a bilayered core having two compartments. In Example 4B, the drug layer combines reboxetine, maltodextrin and stearic acid, and another layer, identified as the push layer, contains hydroxypropylmethylcellulose, which is hydrophilic and soluble in water and the barrier layer contains ethyl cellulose and stearic acid. Thus, Seroff et al. do not contain a water insoluble or partially water insoluble cellulose in the same layer as the maltodextrin, as alleged in the Office Action. Moreover, the sustained release polymer, the drug, the water insoluble or partially water insoluble cellulose such as ethyl cellulose and the maltodextrin are in different layers. They are all not present together in the core so that they can interact with each other, as claimed. Thus, Seroff et al. do not teach disclose or suggest the arrangement of elements, as claimed. Therefore, Seroff et al. do not anticipate the present invention. Consequently, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claim 38, 43, 44, 44, 46, 47, 54-56, 59, 60, 63-66 and 71-71 under 35 U.S.C. § 103 the Office Action cites Shah et al.

The Office Action refers to the formulations in Table 1 and 2 of Shah et al. alleging that the compositions therein render obvious the present invention.

Applicant respectfully disagrees. Tables 1 and 2 of Shah et al. refer to the composition described in Examples 1 and 2, respectively. The composition of Table 1 consists of two layers, an immediate release and a sustained release acetaminophen. The immediate release portion contains drug, maltodextrin and PVP, while the coat contains drug, the sustained release polymer, and is mixed with microcrystalline cellulose. Thus, the maltodextrin and microcrystalline cellulose are both not present in the core, but just as importantly, they are not in the same layer, so that they cannot interact with each other. Further, the maltodextrin is not in the same layer as the sustained release polymer, so that it cannot interact with the microcrystalline cellulose and the sustained release polymer. In other words, the drug, the sustained release polymer, the cellulose which is partly or fully insoluble in water and maltodextrin are not located in one layer so that they can interact with one another, i.e., they are not all present together in a mixture comprising these four elements. Shah et al. do not teach, disclose or even suggest the presence of these ingredients together in one layer, the core, as claimed. Thus, Shah et al. do not teach, disclose or suggest the present invention. Therefore, this rejection under 35 U.S.C. § 103 is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 40-44, 46-48, 54-56, 59, 60, 63-66 and 71-73 the Office Action cites Shah et al. and Mulye et al.

Applicant reiterates its comments with respect to Shah et al. As described hereinabove, Shah et al. do not teach, disclose or suggest the maltodextrin the drug, the sustained release polymer and the water insoluble or partially insoluble cellulose present in the same layer, in the core.

Mulye et al. do not overcome this deficiency.

Mulye et al. disclose a solid sustained release pharmaceutical tablet for administering to a host, comprising a therapeutically effective amount of a pharmaceutically active ingredient and a sustained release carrier, the sustained release carrier comprising (a) a hydrocolloid selected from the group consisting of xanthan gum, guar gum and alginic acid or a pharmaceutically acceptable salt thereof and (b) a cellulose ether, said hydrocolloid and cellulose ether being present in synergistic effective amounts to retard the release of the pharmaceutically active ingredient. The Office Action alleges that Mulye et al. disclose therein a filler such as microcrystalline cellulose, referring to Column 7, Lines 3-17 of Mulye et al.

The Office Action alleges that Shah et al. do not disclose xanthan gum in conjunction with a cellulose ether as the sustained release material or the use of silicified MCC. It cites Mulye for its teaching of a sustained release component comprising xanthan gum and a cellulose ether. Even if the sustained release carrier in the composition of Shah et al. were replaced with xanthan gum and cellulose ether, and the microcrystalline cellulose in Shah et al. were replaced with silicified MCC, the combination does not teach, disclose or suggest the present invention. As indicated hereinabove in Shah et al., the maltodextrin is in a different layer than the microcrystalline cellulose, the sustained release polymer and drug. More specifically, the maltodextrin is present with the uncoated acetaminophen, which the microcrystalline cellulose, the sustained release polymer and drug are in the coat. Thus, even if the sustained release polymer of Shah et al. were substituted with xanthan gum and cellulose ether, the maltodextrin would still not be in the same layer as the microcrystalline cellulose and the sustained release polymer and the drug. Thus, the combination would suggest that, the maltodextrin would be in a different layer from the microcrystalline cellulose. Consequently, the

maltodextrin, for example, could not interact with the microcrystalline cellulose. Therefore, the combination of Shah et al. and Mulye does not teach, disclose or suggest the present invention.

Thus, for the reasons provided, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 43, 44, 46-48, 54-56, 59, 60, 63 and 73 under 35 U.S.C. § 103, the Office Action cites Shah et al. and Tobyn et al.

Applicant reiterates its comments hereinabove with respect to Shah et al., the contents of which are incorporated by reference.

Tobyn et al. teach that there is no chemical or polymorphic difference between a sample of MCC and SMCC, indicating that the silicification process produces a material which is chemically and physically very similar to standard MCC.

Tobyn et al. do not overcome the deficiencies of Shah et al. described hereinabove. As described hereinabove, Shah et al. suggest the presence of maltodextrin in a different layer than the microcrystalline cellulose, drug and sustained release polymer, the latter components being in the coat. Since Tobyn et al. merely disclose that there is no discernible chemical or polymorphic difference between silicified microcrystalline cellulose and standard grade microcrystalline cellulose, Tobyn et al. do not address the deficiency described hereinabove. Moreover, the combination would suggest SMCC, the drug and the hydrophilic polymer in the coat and the uncoated layer comprised of the drug and the maltodextrin mixed together. Thus, the applicant respectfully submits that the combination of the two references suggests a composition wherein the maltodextrin is not in the same layer as the drug, the water insoluble or partial water insoluble cellulose, and the sustained release polymer. Furthermore, the combination does not teach, disclose or suggest maltodextrin interacting with the sustained

release polymer, the drug and the water insoluble or partially water soluble cellulose. The combination does not teach, disclose or suggest a matrix where the active component, the water insoluble or partially water insoluble cellulose, maltodextrin and a sustained release carrier are present in the core, as presently claimed. Thus, this rejection is obviated, withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 43-47, 34-50, 59, 60, 63-66 and 71-73, the Office Action cite Shah et al. and further in view of Shell et al.

Applicant reiterates the comments hereinabove with respect to Shah et al., the contents of which are incorporated by reference.

Shell et al. disclose oral dosage forms of drugs by incorporating them into polymeric matrixes comprised of hydrophilic polymers that swell upon imbibition of water to a size which is large enough to promote retention of the dosage form in the stomach during the feed mode. Examples of hydrophilic polymers include cellulose polymers and their derivatives, microcrystalline cellulose and xanthan gum. The Office Action refers to Example 4 of Shell et al. which discloses metformin controlled release dosage forms with various polymers such as xanthan gum, HPMC, hydroxyethyl cellulose and polyethylene oxide. Magnesium stearate may be included in the various formulations. The Office Action also refers to Example 10, which discloses a metformin dosage from comprising metformin, PEO, magnesium stearate and a coating comprised of HPMC.

However, Shell et al. do not disclose the inclusion of maltodextrin in the pharmaceutical composition.

The Office Action is citing Shell et al. for its teaching of the use of metformin as a drug.

It is respectfully submitted that even if combined in the manner suggested the combination does not overcome the deficiency referred to hereinabove or teach, disclose or suggest the present invention.

Shell et al. do not disclose the inclusion of maltodextrin in the pharmaceutical composition.

Thus, the combination would suggest that the maltodextrn is not blended together with the sustained release polymer, the drug and the water insoluble or partial water insoluble cellulose in the core in the pharmaceutical composition. According to Shah et al., the maltodextrin is in the immediate release formulation and not with the sustained release formulation, which is present in the coat. The coat does not contain any maltodextrin. Thus, again there is no interaction between the aforementioned components and especially the cellulose ether which is partially or wholly insoluble in water and maltodextrin, as claimed. Therefore, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 38, 40-47, 54-56, 59, 60, 63-66 and 71-73 under 35 U.S.C. § 103(a), the Office Action cites Seroff et al. and Shell et al.

Applicant reiterates its comments regarding Seroff et al., the contents of which are incorporated herein by reference, including the comments regarding Example 4B therein. Seroff et al in Example 4B refers to an internal compartment comprising a bilayered compressed core with a drug layer and a push layer, where the drug layer comprises, *inter alia*, roboxetine and maltodextrin and the push layer comprises polyethylene oxide, hydroxypropylmethylcellulose, which is water soluble and a barrier layer containing ethyl cellulose. Thus Seroff et al. do not disclose in Example 4B a water insoluble or partial water insoluble cellulose together in the same layer as the drug, the maltodextrin and the sustained release hydrophilic polymer. Further,

Seroff et al. do not have the drug, and the maltodextrn, the cellulose and the sustained release polyme all mixed together in one layer so that they interact with one another. Moreover, these components are not present in the core, as claimed. As a result, the maltodextrin, for example, cannot retard the release of the drug. When the maltodextrin is a different layer, there is no interaction between it and the drug, the cellulose ether and the hydrophilic sustained release polymer.

Shell et al. do not overcome this deficiency. The Office Action is citing Shell et al. for substituting for the hydrophilic polymer for the sustained release polymer in the coat. However, this would mean a substitution of the cellulose ethers in the push layer with the hydrophilic polymer of Shell et al. indicated hereinabove. Thus, even if combined, maltodextrin and the cellulose ether are in different layers, and thus they are all not in one layer, e.g., the core. Thus, the combination does not teach, disclose or suggest that the maltodextrn is mixed with the sustained release carrier, the water insoluble or partial water insoluble cellulose and the drug in one layer, as claimed. Thus for the reasons provided this rejection is overcome.

Pursuant to the rejection of Claim 38, 40-48, 54-56, 59, 60, 63-73 the Office Action cites Seroff et al. and Shell et al. and Tobyn et al.

Applicant reiterates the comments hereinabove with respect to Serotl et al. and Shell et al., the contents of which are incorporated by reference.

The Office Action is citing Tobyn et al. for the alleged substitution or equivalence of SMCC for microcrystalline cellulose.

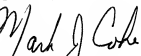
The arguments presented hereinabove regarding Seroff et al. and Shell et al. are applicable. Tobyn et al. do not address the inadequacies of Seroff et al. and Shell et al. It merely discloses that there is no discernable chemical or polymorphic difference between

microcrystalline cellulose and silicified microcrystalline cellulose. Thus, Tobyn et al. do not address the deficiency of Shell et al. and Seroff et al. described hereinabove. The combination would at best suggest substituting silicified microcrystalline cellulose for microcrystalline cellulose. Accordingly, the combination would suggest a push layer containing a soluble cellulose ether, the barrier layer containing ethyl cellulose, and the drug layer to contain the drug and maltodextrin. The combination of Seroff et al. and Shell et al. and Tobyn et al. do not teach, disclose or suggest a sustained release formulation wherein the drug, the sustained release hydrophilic polymer, maltodextrin and the water insoluble or partially water soluble cellulose are all present in the core, as claimed. Further, there is no interaction between the microcrystalline cellulose and, for example, the cellulose ether.

Accordingly, for the reasons provided, this rejection is overcome; withdrawal thereof is respectfully requested.

Thus, in view of the Amendment to the Claims and the Remarks it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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